=> d ibib abs ind 2-3

L4 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:814679 HCAPLUS
DOCUMENT NUMBER: 137:289038
TITLE: **Nitric oxide** donors for inducing neurogenesis
INVENTOR(S): **Chopp, Michael; Zhang, Rui Lan**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp., Cont.-in-part of U.S. Ser. No. 18,201.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002155173	A1	20021024	US 2002-75715	20020213
WO 2000076318	A1	20001221	WO 2000-US16353	20000614

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1999-138971P P 19990614
WO 2000-US16353 W 20000614
US 2002-18201 A2 20020402

AB There is provided a method of promoting neurogenesis by administering a therapeutic amount of a **nitric oxide** donor compound to a patient in need of neurogenesis promotion. Also provided is a compound for providing neurogenesis having an effective amount of a **nitric oxide** donor sufficient to promote neurogenesis. A **nitric oxide** compound for promoting neurogenesis is also provided. Further, a method of augmenting the production of brain cells and facilitating cellular structural and receptor changes by administering an effective amount of a **nitric oxide** donor compound to a site in need of augmentation is provided. There is provided a method of increasing both neurol. and cognitive function by administering an effective amount of a **nitric oxide** donor compound to a patient.

IC ICM A61K031-519
ICS A61K031-198; A61K033-00
INCL 424718000
CC 1-11 (Pharmacology)
ST **nitric oxide** donor neurogenesis
IT Brain
(neurogenesis; **nitric oxide** donors for inducing neurogenesis)
IT Cognition enhancers
Human
Neurogenesis
Neuron
(**nitric oxide** donors for inducing neurogenesis)
IT 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; **nitric oxide** donors for inducing neurogenesis)
IT 10102-43-9, **Nitric oxide**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nitric oxide** donors for inducing neurogenesis)
IT 74-79-3, L-Arginine, biological studies 134523-03-8, Lipitor 139755-83-2, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nitric oxide** donors for inducing neurogenesis)

L4 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:900390 HCAPLUS
DOCUMENT NUMBER: 134:37045
TITLE: **Nitric oxide** donors for inducing neurogenesis
INVENTOR(S): **Chopp, Michael; Zhang, Rui Lan**
PATENT ASSIGNEE(S): Henry Ford Health System, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000076318	A1	20001221	WO 2000-US16353		20000614
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2377373	AA	20001221	CA 2000-2377373		20000614
AU 2000054882	A5	20010102	AU 2000-54882		20000614
AU 782283	B2	20050714			
EP 1233670	A1	20020828	EP 2000-939866		20000614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
JP 2003532622	T2	20031105	JP 2001-502674		20000614
NZ 516513	A	20040326	NZ 2000-516513		20000614
ZA 2001010305	A	20020923	ZA 2001-10305		20011214
US 2002155173	A1	20021024	US 2002-75715		20020213
PRIORITY APPLN. INFO.:			US 1999-138971P	P	19990614
			WO 2000-US16353	W	20000614
			US 2002-18201	A2	20020402

AB A method is provided for promoting neurogenesis by administering a therapeutic amount of a **nitric oxide** donor compound to a patient in need of neurogenesis promotion. Also provided is a compound for providing neurogenesis having an effective amount of a **nitric oxide** donor sufficient to promote neurogenesis. A **nitric oxide** compound for promoting neurogenesis is also provided. Further, a method of augmenting the production of brain cells and facilitating cellular structural and receptor changes by administering an effective amount of a **nitric oxide** donor compound to a site in need of augmentation is provided. A method is provided for increasing both

neurol. and cognitive function by administering an effective amount of a **nitric oxide** donor compound to a patient.

IC ICM A01N037-00
ICS A01N037-12; A01N037-44; A61K031-21; A61K031-195

CC 1-11 (Pharmacology)

ST **nitric oxide** donor neurogenesis induction; neurol cognitive function **nitric oxide** donor; brain cell prodn **nitric oxide** donor

IT Brain
(dentate gyrus, granule cell layer; **nitric oxide** donors for inducing neurogenesis)

IT Brain
(dentate gyrus; **nitric oxide** donors for inducing neurogenesis)

IT Brain
(hippocampus; **nitric oxide** donors for inducing neurogenesis)

IT Brain, disease
(ischemia; **nitric oxide** donors for inducing neurogenesis)

IT Behavior
(motor; **nitric oxide** donors for inducing neurogenesis)

IT Nerve
(neurogenesis; **nitric oxide** donors for inducing neurogenesis)

IT Nerve
(neuron; **nitric oxide** donors for inducing neurogenesis)

IT Brain
Cognition enhancers
Nervous system agents
(**nitric oxide** donors for inducing neurogenesis)

IT Brain
(olfactory bulb; **nitric oxide** donors for inducing neurogenesis)

IT Behavior
(psychomotor; **nitric oxide** donors for inducing neurogenesis)

IT Brain
(rostral migratory stream; **nitric oxide** donors for inducing neurogenesis)

IT Brain, disease
(stroke; **nitric oxide** donors for inducing neurogenesis)

IT Brain
(subventricular zone; **nitric oxide** donors for inducing neurogenesis)

IT 9025-82-5, Phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **nitric oxide** donors for inducing neurogenesis)

IT 74-79-3, L-Arginine, biological studies 67776-06-1, SNAP 146724-94-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nitric oxide** donors for inducing neurogenesis)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**nitric oxide** donors for inducing neurogenesis)

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=> d que stat l18
L6             3 SEA FILE=REGISTRY ABB=ON  (DETANONOATE OR PAPANONOATE OR
                 S-NITROSO-N-ACETYLPENICILLAMINE OR SODIUM NITROPRUSSIDE OR
                 SODIUM NITROGLYCERINE OR PHOSPHODIESTERASE INHIBITORS OR
                 L-ARGININE)/CN
L7         76296 SEA FILE=HCAPLUS ABB=ON  L6 OR ?DETANONOATE? OR ?PAPANONOATE?
                 OR S(W)?NITROSO?(W)N(W)?ACETYLPENICILLAMIN? OR ?PHOSPHODIESTERA
                 S?(W)?INHIBIT? OR L(W)?ARGININE?
L8             1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L9         20263 SEA FILE=HCAPLUS ABB=ON  L7 AND (L8 OR ?NITRIC?(W)?OXID?)
L15         1081 SEA FILE=HCAPLUS ABB=ON  L9 AND (?NEURON?(3A)?GROW? OR
                 ?AUGMENT?)
L17           14 SEA FILE=HCAPLUS ABB=ON  L15 AND ?STROKE?
L18            8 SEA FILE=HCAPLUS ABB=ON  L17 AND (PRD<19990614 OR PD<19990614)

=> d ibib abs l18 1-8

L18  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:756765  HCAPLUS
DOCUMENT NUMBER:          130:119339
TITLE:                    Increased aortic blood pressure contributes to
                          potentiated dobutamine inotropic responses after
                          systemic NO synthase inhibition in sheep
AUTHOR(S):                Penny, Daniel J.; Chen, Hong; Smolich, Joseph J.
CORPORATE SOURCE:         Institute of Reproduction and Development, Monash
                          University, Clayton, Australia
SOURCE:                   Cardiovascular Research (1998), 40(2),
                          282-289
                          CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER:                Elsevier Science B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Objective: To determine whether inotropic responses to the β-adrenergic
     agonist dobutamine are potentiated by systemic inhibition of
     nitric oxide synthase (NOS) with the L-
     arginine analog Nω-nitro- L-arginine
     (L-NNA), and to establish to what extent any observed responses are related
     to the increase in aortic blood pressure accompanying systemic NOS
     inhibition.  Methods: Dobutamine was infused incrementally at rates of 1,
     2.5, 5 and 10 μg/kg/min in 15 open-chest, anesthetized ewes before and
     after inhibition of NO synthesis with i.v. L-NNA (n=8), or elevation of
     mean aortic blood pressure to the same extent as attained with NOS
     inhibition using proximal arterial occlusion (n=7).  Results: By the peak
     infusion rate, dobutamine increased the maximal rate of rise of left
     ventricular pressure (LV dP/dtMAX) by 100% (p<0.001) and reduced LV
     stroke work by 18% (p<0.01).  L-NNA and arterial occlusion
     increased resting mean aortic blood pressure by 55±4 and 51±3 mmHg
     resp.  Compared to dobutamine alone, subsequent peak dobutamine-related
     increases in LV dP/dtMAX were augmented by 76% after L-NNA and
     by 88% after arterial occlusion (both p<0.001).  Moreover, dobutamine
     increased LV stroke work by 23% at infusion rates of 1-5
     μg/kg/min (p<0.001) after L-NNA, and by 17% at an infusion rate of 1
     μg/kg/min (p<0.01) after arterial occlusion.  Conclusions: Systemic NOS
     inhibition potentiates the effects of dobutamine on LV isovolumic and
     pumping performance in the intact circulation, but this potentiation is in
     large part related to the increase in arterial blood pressure accompanying
     NOS inhibition.
REFERENCE COUNT:          40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L18 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:12623 HCAPLUS
DOCUMENT NUMBER: 128:87244
TITLE: Regional renal **nitric oxide** release in **stroke**-prone spontaneously hypertensive rats
AUTHOR(S): Zuckerman, Andrea; Chander, Praveen N.; Zeballos, Guillermo A.; Stier, Charles T., Jr.
CORPORATE SOURCE: Department of Pediatrics, New York Medical College, Valhalla, NY, 10595, USA
SOURCE: Hypertension (Dallas) (**1997**), 30(6), 1479-1486
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Diminished **nitric oxide** (NO) production has been implicated in the pathogenesis of salt-sensitive hypertension. We questioned whether such a defect is responsible for the malignant hypertension and nephrosclerosis in **stroke**-prone spontaneously hypertensive rats (SHRSP) fed a high-salt/**stroke**-prone diet (S) vs. a regular diet (R). NO release from 30-min incubates of cortex and outer and inner medulla were studied in SHRSP at 10, 12, and 16 wk of age on the S diet vs. R diet. SHRSP-S exhibited a marked age-dependent increase in NO release, especially in the cortex. Increases were only modest in SHRSP-R. At 16 wk, cortical NO was 93 vs. 6 pmol/mg tissue in SHRSP-S vs. SHRSP-R. Immunohistochem. staining increased mostly for neuronal, slightly for endothelial, and negligibly for inducible isoforms of NO synthase and was predominantly in the cortex of SHRSP-S vs. SHRSP-R. Despite similar hypertension in SHRSP-S vs. SHRSP-R (mean arterial pressure, 174 vs. 177 mm Hg), malignant nephrosclerosis was seen only in SHRSP-S, affecting 22% of glomeruli and 23 vessels per 100 glomeruli by 16 wk. Nω-nitro- **L-arginine** (15 mg/kg per day) in SHRSP-S abrogated the increase in cortical NO but further **augmented** the hypertension and accelerated lesion development. Wistar-Kyoto rats at 16 wk on the R diet had NO levels similar to those of SHRSP-R, showed increased cortical NO to only 28 pmol/mg on the S diet, but remained normotensive and lesion-free. We conclude that hypertension and lesion development in SHRSP are not due to deficient renal NO. Accelerated onset of malignant nephrosclerosis by NO synthase inhibition suggests that NO is protective in these animals, mitigating the effects of hypertension and S diet on renal pathol.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:493907 HCAPLUS
DOCUMENT NUMBER: 127:174771
TITLE: Role of **nitric oxide** in the contractile response to 5-hydroxytryptamine of the basilar artery from Wistar Kyoto and **stroke**-prone rats
AUTHOR(S): Salomone, Salvatore; Morel, Nicole; Godfraind, Theophile
CORPORATE SOURCE: Laboratoire de Pharmacologie, Universite Catholique de Louvain, Brussels, B-1200, Belg.
SOURCE: British Journal of Pharmacology (**1997**), 121(6), 1051-1058
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Isolated basilar arteries from spontaneously hypertensive **stroke**-prone rats (SHRSP) are more sensitive to the contractile effect of 5-hydroxytryptamine (5-HT) than those from normotensive Wistar Kyoto rats (WKY). This has been attributed to a different proportion of 5-HT receptor subtypes mediating these responses. In the present study the authors have examined if differences in **nitric oxide** release could also contribute to this difference in sensitivity to 5-HT. At rest, the normalized internal diameter was significantly smaller in SHRSP (297.4 μm) than in WKY (375.1 μm) arteries. The contractile response to 100 mM KCl was higher in WKY (3.57 mN mm-1) than in SHRSP arteries (2.32 mN mm-1). When added on the plateau of contraction to 5-HT (1 μM), acetylcholine (ACh, 3 μM) evoked significant relaxation in all prepns. from WKY, but only in 15 out of 26 prepns. from SHRSP. The mean relaxations were 55.4% in WKY and 20.6% in SHRSP (as % of the contractile tone evoked by 5-HT). The NO synthase inhibitor Nω-nitro- **L-arginine** (L-NOARG, 0.1 mM) produced a similar increase in tone in both WKY and SHRSP. This tone was equal (in % of the contractile response to 100 mM KCl) to 70.8% in WKY and 67.6% in SHRSP and was reversed by **L-arginine** (1 mM) and by 1,4-dihydropyridine calcium channel blockers (10 nM nisoldipine, 10 nM lacidipine, 100 nM nifedipine). The L-NOARG-induced tone was absent when the arteries were bathed in phosphate-free Krebs (pH 7.4). EC50 values of 5-HT were about four fold smaller in SHRSP than in WKY arteries. The maximal response to 5-HT (Emax) was higher than 100 mM KCl-contraction in SHRSP but not in WKY arteries. Removal of endothelium produced a shift to the left of the 5-HT curve in WKY, but not in SHRSP arteries. When evoked in phosphate-free Krebs, the contractile responses to 5-HT showed tachyphylaxis, but the responses were reproducible by adding the agonist at 30 min intervals. In such conditions, EC50 values of 5-HT were about two fold smaller in SHRSP than in WKY arteries. In phosphate-free Krebs, the blockade of NO synthase did not change the contractile response to 100 mM KCl; it reduced EC50 and increased Emax of 5-HT in WKY, but not in SHRSP. These results confirm that the sensitivity to 5-HT is higher in basilar artery isolated from SHRSP than in those from WKY. They show that endothelium-dependent vasorelaxation to ACh is impaired in SHRSP. The finding that removal of endothelium or blockade of NO synthase **augmented** the contractile response to 5-HT in WKY, but not in SHRSP basilar arteries indicates that the difference in responsiveness to 5-HT observed between WKY and SHRSP basilar arteries might be, at least in part, related to dissimilarities in NO release. Furthermore, the L-NOARG-induced contraction sensitive to calcium channel blockers indicates that, in basilar arteries, NO production might lower L-type calcium channel opening and thereby control the tone of the vessels.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:283184 HCAPLUS
DOCUMENT NUMBER: 126:311943
TITLE: Tissue variation of acute hemodynamic changes [induced] by NG-nitro-**L-arginine** in **stroke**-prone spontaneously hypertensive and Wistar-Kyoto rats
AUTHOR(S): Higashino, H.; Simeonova, K.; Lambev, I.; Suzuki, A.
CORPORATE SOURCE: Department of Pharmacology, Kinki University School of Medicine, Osaka, 589, Japan
SOURCE: Clinical and Experimental Pharmacology and Physiology

(**1997**), 24(3/4), 249-255
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acute effects of NO synthase inhibition on hemodynamics in **stroke**-prone spontaneously hypertensive (SHRSP) and normotensive Wistar-Kyoto (WKY) rats were investigated by using radiolabeled microspheres. I.v. administration of NG-nitro-**L-arginine** (L-NNA) (3 and 6 mg/kg) increased total peripheral resistance, decreased cardiac output and increased blood pressure in both SHRSP and WKY rats. Decreases in regional blood flow in the lung, muscle and stomach of WKY rats were observed following L-NNA administration. At 6 mg/kg, L-NNA produced a 70% increase in brain regional blood flow only in SHRSP. Thus, there are variations in the involvement of NO in different tissues. The hypertension in SHRSP **augments** NO-mediated vasodilation.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:317286 HCAPLUS
DOCUMENT NUMBER: 122:96981
TITLE: Endothelium-dependent contractions induced by acetylcholine in renal arteries isolated from Wistar-Kyoto (WKY) and **stroke**-prone spontaneously hypertensive (SHRSP) rats
AUTHOR(S): Nishimura, Yoshitaka; Suzuki, Aritomo; Miyatake, Rie; Nakai, Yoshihiro; Koh, Tosei
CORPORATE SOURCE: School Medicine, Kinski Univ., Osaka, Japan
SOURCE: Kinki Daigaku Igaku Zasshi (**1994**), 19(4, Suppl.), 35-8
CODEN: KDIZDD; ISSN: 0385-8367
PUBLISHER: Kinki Daigaku Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The authors examined the contractile responses to acetylcholine (ACh) in isolated renal artery rings obtained from WKY and SHRSP at 3 and 6 mo of age. ACh caused a transient contraction in endothelium-intact renal arteries from WKY and SHRSP. ACh-induced contraction was abolished by removal of the endothelium, and was **augmented** by pretreatment with NG-nitro-**L-arginine** (NOARG) in both groups. Indomethacin completely inhibited ACh-induced contraction in NOARG-treated arteries of WKY and SHRSP. Contraction induced by ACh was significantly smaller in SHRSP at 3 and 6 mo of age than in age-matched WKY. ACh-induced endothelium-dependent relaxation in renal arteries precontracted with phenylephrine was decreased in SHRSP at 3 and 6 mo of age when compared to age-matched WKY. Relaxation induced by ACh was inhibited by NOARG in both groups. These results suggest that ACh produces both contractile responses mediated by cyclooxygenase products and relaxation responses mediated by **nitric oxide** in an endothelium-dependent manner, and that these responses were impaired in SHRSP.

L18 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:262838 HCAPLUS
DOCUMENT NUMBER: 122:46065
TITLE: Endothelial dysfunction in aorta of the spontaneously hypertensive, **stroke**-prone rat: effects of therapy with verapamil and trandolapril alone and in

combination
AUTHOR(S): Novosel, Dragutin; Lang, Markus G.; Noll, Georg; Luescher, Thomas F.
CORPORATE SOURCE: Dep. Med., Univ. Hospitals Basel, Basel, Switz.
SOURCE: Journal of Cardiovascular Pharmacology (**1994**), 24(6), 979-85
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of chronic therapy with the angiotensin-converting enzyme (ACE) inhibitor trandolapril and/or Ca2+ antagonist verapamil on endothelial and vascular smooth muscle (VSM) function were studied in spontaneously hypertensive, **stroke**-prone rats (SHR-SP). Dosages decreasing systolic blood pressure (SBP) by 20% were administered orally (p.o.) by gavage as a monotherapy or combination therapy for 8 wk, beginning at age 6 wk. Combination therapy dosages were the same as thosed used in monotherapy (trandolapril 0.7 mg/kg day verapamil 20 mg/kg/day) in one group; the second group received only half the monotherapy dosage. The study was placebo-controlled and performed in parallel groups. Isometric tension was measured in aortic rings suspended in organ chambers (95% C2/5% CO2; 37°C). SBP decreased in all groups, as compared with placebo [30-47 mm Hg, anal. of variance (ANOVA), $p < 0.05$], but decrease was more pronounced in rats receiving high-dose combination (76 mm Hg, ANOVA, $p < 0.05$). In norepinephrine (NE)-contracted rings, endothelium-dependent relaxation to acetylcholine (ACh) was **augmented** similarly with all forms of therapy (maximal relaxations 89-94%) as compared with placebo (64 ± 6%, $p < 0.05$). In contrast, the response to sodium nitroprusside (SNP) was similar in all groups (NS). In quiescent rings, ACh elicited endothelium-dependent contractions (in the presence of Nω-monomethyl- **L-arginine**, L-NAME) that were not affected by therapy. In rings of untreated SHR-SP incubated with a thromboxane receptor antagonist (SQ 30741), the reduced endothelium-dependent relaxation to ACh was corrected, indicating that the main effect must be an increase in release of **nitric oxide** (NO) relative to that of thromboxane (TXA2)/prostaglandin H2 (PGH2). Both antihypertensive therapy with a combination of ACE inhibitor and Ca2+ antagonist at low dosage and monotherapy have comparable effects on BP pressure and endothelial function.

L18 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:406428 HCAPLUS
DOCUMENT NUMBER: 121:6428
TITLE: Modulation of contraction of aortic smooth muscle by endothelium and its decrease in spontaneously hypertensive rats
AUTHOR(S): Sunano, Satoru; Kaneko, Kyoko; Yamamoto, Kazuo; Sasaki, Fumiko
CORPORATE SOURCE: Res. Inst. Hypertens., Kinki Univ., Osaka, Japan
SOURCE: Kinki Daigaku Igaku Zasshi (**1993**), 18(4,SUPPL), 65-7
CODEN: KDIZDD; ISSN: 0385-8367
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Noradrenaline-induced contraction was potentiated by the removal of endothelium and the potentiation was greater in the aorta of Wistar Kyoto (WKY) rats than in that of **stroke**-prone spontaneously hypertensive rats (SHRSP). NG-nitro-**L-arginine** (L-NNA, 100 μM), which inhibits **nitric oxide** (NO) synthesis, also potentiated the noradrenaline-induced contraction in the

endothelium-intact preparation The effect of L-NNA was greater in the WKY preparation Acetylcholine-induced relaxation in the endothelium-intact aorta was impaired in the SHRSP preparation Phenylephrine- and clonidine-induced contractions were **augmented** by pretreatment with L-NNA or removal of endothelium. Apparently, the vascular endothelium modulates the noradrenaline-induced contraction by releasing NO through α1- and α2-adrenergic receptors. The depression of noradrenaline-induced contraction by the endothelium was **augmented** by the repetition of the initiation of the contraction. The **augmentation** of the depression was less prominent in the SHRSP aorta. This also suggests that the release of NO through these adrenergic receptors is reduced in the aorta of SHRSP.

L18 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:75470 HCAPLUS
DOCUMENT NUMBER: 114:75470
TITLE: Effects of NG-nitro-**L-arginine** methyl ester or indomethacin on differential regional and cardiac hemodynamic actions of arginine vasopressin and lysine vasopressin in conscious rats
AUTHOR(S): Gardiner, Sheila M.; Compton, Alix M.; Kemp, Philip A.; Bennett, Terence
CORPORATE SOURCE: Med. Sch., Nottingham Univ., Nottingham, NG7 2UH, UK
SOURCE: British Journal of Pharmacology (**1991**), 102(1), 65-72
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Measurements of changes in renal, mesenteric, and hindquarter hemodynamics or cardiac hemodynamics in response to i.v. bolus doses of AVP or lysine vasopressin (LVP, 0.7 and 7.0 pmol) were made in conscious, chronically-instrumented Long-Evans rats. In some expts. AVP and LVP were administered during an infusion of NG-nitro-**L-arginine** Me ester (L-NAME; 1.0 or 0.3 mg/kg/h) to determine whether or not inhibition of NO production influenced the cardiovascular effects of the peptides. In other expts., indomethacin (bolus dose of 5 mg/kg followed by infusion at 5 mg/kg/h) was given to determine the possible involvement of cyclooxygenase products in the responses to AVP and LVP. Under control conditions, the lower dose of LVP had greater effects than AVP on heart rate, mean arterial blood pressure, renal, mesenteric, and hindquarter conductances, total peripheral conductance, cardiac index, peak aortic flow, and +dF/dtmax. The higher dose of LVP had greater effects than AVP on all variables (i.e. including **stroke** index and central venous pressure). In the presence of L-NAME (1 mg/kg/h) there was a sustained increase in mean arterial blood pressure (+ 23 mmHg) and redns. in mesenteric (-38%) and hindquarter (-30%) vascular conductances. Under these conditions the difference in the pressor effects of AVP and LVP was abolished, but their differential effects on regional and cardiac hemodynamics persisted. This dose of L-NAME did not change cardiac baroreflex sensitivity. During infusion of L-NAME at a lower rate (0.3 mg/kg/h) baseline cardiovascular status was unchanged and regional hemodynamic effects of AVP and LVP were enhanced, but the differences in the regional vasoconstrictor responses to the 2 peptides persisted. Indomethacin (5 mg/kg bolus, then 5 mg/kg/h infusion) **augmented** the renal vasoconstrictor responses to AVP and LVP, but abolished the difference in the hindquarter vasoconstrictor responses to the 2 peptides. However, the differences in the pressor and the renal and mesenteric vasoconstrictor effects of AVP and LVP still occurred in the presence of indomethacin. Evidently, AVP normally has lesser cardiovascular effects than LVP but this difference does not seem to be due to more effective

stimulation of NO-mediated or cyclooxygenase-dependent vasodilator mechanisms by AVP than LVP.

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=> d que stat l20
L6             3 SEA FILE=REGISTRY ABB=ON  (DETANONOATE OR PAPANONOATE OR
                 S-NITROSO-N-ACETYLPENICILLAMINE OR SODIUM NITROPRUSSIDE OR
                 SODIUM NITROGLYCERINE OR PHOSPHODIESTERASE INHIBITORS OR
                 L-ARGININE)/CN
L7         76296 SEA FILE=HCAPLUS ABB=ON  L6 OR ?DETANONOATE? OR ?PAPANONOATE?
                 OR S(W)?NITROSO?(W)N(W)?ACETYLPENICILLAMIN? OR ?PHOSPHODIESTERA
                 S?(W)?INHIBIT? OR L(W)?ARGININE?
L8             1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L9         20263 SEA FILE=HCAPLUS ABB=ON  L7 AND (L8 OR ?NITRIC?(W)?OXID?)
L15         1081 SEA FILE=HCAPLUS ABB=ON  L9 AND (?NEURON?(3A)?GROW? OR
                 ?AUGMENT?)
L17           14 SEA FILE=HCAPLUS ABB=ON  L15 AND ?STROKE?
L19           45 SEA L17
L20           21 DUP REMOV L19 (24 DUPLICATES REMOVED)

L20  ANSWER 1 OF 21     MEDLINE on STN
ACCESSION NUMBER:    2005650300     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 16275194
TITLE:               Effect of sildenafil on cardiac performance in patients
                     with heart failure.
AUTHOR:              Hirata Kozo; Adji Audrey; Vlachopoulos Charalambos;
                     O'Rourke Michael F
CORPORATE SOURCE:    St. Vincent's Clinic, University of New South Wales,
                     Sydney, Australia.
SOURCE:              The American journal of cardiology, (2005 Nov 15) 96 (10)
                     1436-40.  Electronic Publication: 2005-09-27.
                     Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RANDOMIZED CONTROLLED TRIAL)
                     (CLINICAL TRIAL)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200602
ENTRY DATE:          Entered STN: 20051216
                     Last Updated on STN: 20060214
                     Entered Medline: 20060213
AB   Sildenafil is rarely used in patients with heart failure despite a high
     prevalence of erectile dysfunction, and the theoretic possibility that by
     increasing nitric oxide availability, it may improve
     left ventricular (LV) load and performance.  This study aimed to determine
     the peak effects of sildenafil on LV load and performance in patients with
     heart failure caused by systolic LV dysfunction.  Twenty patients with
     controlled LV failure and ejection fractions <35% received sildenafil 50
     mg or a matching placebo when not receiving regular medication for > or
     =12 hours, in a randomized, placebo-controlled, double-blind, 2-way
     crossover fashion.  Cardiac output was measured by Doppler
     echocardiography.  The aortic pressure waveform was determined using
     generalized transfer function from radial artery applanation tonometry.
     Aortic and femoral arterial stiffness was determined as carotid-femoral
     and femoral-pedal pulse-wave velocity (PWV); wave reflection was measured
     as an augmentation index (AIx).  Cardiac index increased
     significantly (by 0.37 L/min.m(2), p <0.0001), with the peak effect 60
     minutes after sildenafil administration.  Compared with the baseline
     value, total systemic resistance showed a reduction of 479 dynes.s.cm(-5)
     (p <0.0001).  Aortic and lower limb PWV decreased significantly (by 0.89
     and 1.14 m/s, respectively, p <0.0001 for both), as did AIx (by 3.6%
     absolute, p <0.0001); these remained significant after adjustment for mean
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pressure and heart rate changes. In conclusion, sildenafil improves cardiac performance because of a decrease in LV load, which is caused by decreases in peripheral resistance, in aortic and large artery stiffness, and in wave reflection from peripheral sites. This can explain the increase in cardiac output and in exercise capacity with sildenafil in patients with heart failure.

L20 ANSWER 2 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004186239 EMBASE
TITLE: Targeting eNOS for **stroke** protection.
AUTHOR: Endres M.; Laufs U.; Liao J.K.; Moskowitz M.A.
CORPORATE SOURCE: M. Endres, Department of Neurology, Charite Hospital, Humboldt University, Schumanstrasse 20/21, D-10117 Berlin, Germany. matthias.endres@charite.de
SOURCE: Trends in Neurosciences, (2004) Vol. 27, No. 5, pp. 283-289. .
Refs: 68
ISSN: 0166-2236 CODEN: TNSCDR
PUBLISHER IDENT.: S 0166-2236(04)00102-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040520
Last Updated on STN: 20040520

AB **Nitric oxide** (NO) generated by endothelial NO synthase (eNOS) plays a crucial role in vascular function and homeostasis. NO possesses vasodilatory, anti-inflammatory, antithrombotic and antiproliferative properties. **Augmentation** of NO production increases cerebral blood flow, which can lead to neuroprotection during brain ischaemia. Several modalities that upregulate eNOS expression and/or activity have recently been identified, including HMG-CoA reductase inhibitors (statins), steroid hormones, nutrients and physical activity. They all increase NO bioavailability, leading to enhanced cerebral blood flow and protection from ischaemic **stroke**. Thus, therapeutic modalities that target eNOS not only serve as preventive measures to reduce **stroke** incidence but also could represent novel treatment strategies for reducing brain injury during cerebral ischaemia.

L20 ANSWER 3 OF 21 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2004305984 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15054117
TITLE: Effect of short-term phytoestrogen treatment in male rats on **nitric oxide**-mediated responses of carotid and cerebral arteries: comparison with 17beta-estradiol.
AUTHOR: Sobey Christopher G; Weiler Jane M; Boujaoude Mirna; Woodman Owen L
CORPORATE SOURCE: Department of Pharmacology, The University of Melbourne, Parkville, Victoria, Australia.. cgsobey@unimelb.edu.au
SOURCE: Journal of pharmacology and experimental therapeutics, (2004 Jul) 310 (1) 135-40. Electronic Publication: 2004-03-30.
Journal code: 0376362. ISSN: 0022-3565.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040624
Last Updated on STN: 20040908
Entered Medline: 20040907

AB The use of estrogen for protection against vascular dysfunction is limited due to its effects on the reproductive system, particularly in males. We postulated that daidzein, an isoflavone with estrogen-like effects on the systemic vasculature but not the reproductive system, might enhance **nitric oxide** (NO)-mediated cerebral vasodilatation.
Male rats were administered vehicle, 17beta-estradiol (0.1 mg/kg s.c.), or daidzein (0.2 mg/kg s.c.) daily for 7 days. Basal and acetylcholine-stimulated NO release was assessed in vitro via carotid arterial rings or in vivo by measuring changes in basilar artery diameter. Levels of protein expression of endothelial NO synthase (eNOS), caveolin-1, and calmodulin were assessed in carotid arteries using Western analysis. Plasma NO levels were doubled by daidzein or 17beta-estradiol. NO production and endothelium-dependent contraction in response to the NOS inhibitor NG-nitro-**L-arginine** (L-NNA; 100 microM) was enhanced by 50 to 100% in carotid arteries from rats treated with daidzein or 17beta-estradiol. Acetylcholine-induced relaxation was selectively enhanced in carotid arteries from rats treated with daidzein. Similarly, constrictor responses of the basilar artery to L-NNA in vivo were selectively **augmented** by approximately 100% by 17beta-estradiol treatment and tended to be approximately 50% greater in daidzein-treated rats. Expression of caveolin-1 was decreased, and calmodulin was increased, in vessels from daidzein- or 17beta-estradiol-treated rats. eNOS expression was unaffected by the treatments. These data suggest that short-term administration of daidzein or 17beta-estradiol modulates cerebral artery reactivity in males by enhancing synthesis and release of endothelium-derived NO. Isoflavone therapy may therefore be a feasible approach to protect against cerebrovascular disease and **stroke**.

L20 ANSWER 4 OF 21 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003157960 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12665476
TITLE: Induction of LOX-1 and iNOS expressions by ischemia-reperfusion of rat kidney and the opposing effect of **L-arginine**.
AUTHOR: Kosaka Hiroaki; Yoneyama Hirohito; Zhang Ling; Fujii Shigemoto; Yamamoto Akira; Igarashi Junsuke
CORPORATE SOURCE: The 2nd Department of Physiology, Kagawa Medical University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.. hkosaka@kms.ac.jp
SOURCE: FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2003 Apr) 17 (6) 636-43.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030406
Last Updated on STN: 20030422
Entered Medline: 20030421

AB Lectin-like oxidized low-density lipoprotein receptor (LOX-1) is a newly

identified endothelial cell surface major receptor for oxidatively modified low-density lipoprotein. Progression of arthrosclerosis in the donor organ after organ transplantation is a major problem. We hypothesized that ischemia-reperfusion induces LOX-1. After 1 h ischemia of bilateral kidneys plus 3, 6, or 12 h reperfusion, we first revealed that LOX-1 mRNA expression was increased in renal cortex and medulla at 6 h after reperfusion, which was decreased by **L-arginine** supplement. Plasma **nitric oxide** (NO) end-product nitrite plus nitrate and inducible **nitric oxide** synthase (NOS) expression were increased after reperfusion of 6 h. However, NOS substrate **L-arginine** did not **augment** but markedly decreased plasma NO end product, because **L-arginine** supplement suppressed inducible NOS expression in kidney. We hypothesized that available **L-arginine** is depleted by ischemia-reperfusion, leading to inducible NOS induction. Ischemia decreased **L-arginine** levels in kidney and **L-arginine** supplement increased NO end products in renal cortex in the earliest phase of reperfusion. These results disclosed for the first time that a deficiency in **L-arginine** by ischemia reperfusion causes uncoupling of constitutive NOS, which induces inducible NOS and LOX-1, implying why **L-arginine** is effective for **stroke** or transplantation in preventing atherosclerotic progress.

L20 ANSWER 5 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2002219535 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11955849
TITLE: The presence of African American race predicts improvement in coronary endothelial function after supplementary **L-arginine**.
AUTHOR: Houghton Jan L; Philbin Edward F; Strogatz David S; Torosoff Mikhail T; Fein Steven A; Kuhner Patricia A; Smith Vivienne E; Carr Albert A
CORPORATE SOURCE: Division of Cardiology, Department of Medicine, Albany Medical College, Albany, New York 12208, USA.. Houghtj@mail.amc.edu
CONTRACT NUMBER: HL-50262 (NHLBI)
SOURCE: Journal of the American College of Cardiology, (2002 Apr 17) 39 (8) 1314-22.
Journal code: 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020417
Last Updated on STN: 20020511
Entered Medline: 20020510

AB OBJECTIVES: The purpose of our study was to determine if the presence of African American ethnicity modulates improvement in coronary vascular endothelial function after supplementary **L-arginine**.
BACKGROUND: Endothelial dysfunction is an early stage in the development of coronary atherosclerosis and has been implicated in the pathogenesis of hypertension and cardiomyopathy. Amelioration of endothelial dysfunction has been demonstrated in patients with established coronary atherosclerosis or with risk factors in response to infusion of **L-arginine**, the precursor of **nitric oxide**.
Racial and gender patterns in **L-arginine** responsiveness have not, heretofore, been studied. METHODS: Invasive testing of coronary artery and microvascular reactivity in response to

graded intracoronary infusions of acetylcholine (ACh) +/- **L-arginine** was carried out in 33 matched pairs of African American and white subjects with no angiographic coronary artery disease. Pairs were matched for age, gender, indexed left ventricular mass, body mass index and low-density lipoprotein cholesterol. RESULTS: In addition to the matching parameters, there were no significant differences in peak coronary blood flow (CBF) response to intracoronary adenosine or in the peak CBF response to ACh before **L-arginine** infusion. However, absolute percentile improvement in CBF response to ACh infusion after **L-arginine**, as compared with before, was significantly greater among African Americans as a group (45 +/- 10% vs. 4 +/- 6%, p = 0.0016) and after partitioning by gender. The mechanism of this increase was mediated through further reduction in coronary microvascular resistance. **L-arginine** infusion also resulted in greater epicardial dilator response after ACh among African Americans. CONCLUSIONS: We conclude that intracoronary infusion of **L-arginine** provides significantly greater **augmentation** of endothelium-dependent vascular relaxation in those of African American ethnicity when compared with matched white subjects drawn from a cohort electively referred for coronary angiography. Our findings suggest that there are target populations in which supplementary **L-arginine** may be of therapeutic benefit in the amelioration of microvascular endothelial dysfunction. In view of the excess prevalence of cardiomyopathy among African Americans, pharmacologic correction of microcirculatory endothelial dysfunction in this group is an important area of further investigation and may ultimately prove to be clinically indicated.

L20 ANSWER 6 OF 21 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002632347 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12390294
TITLE: Responses to endothelium-derived factors and their interaction in mesenteric arteries from Wistar-Kyoto and **stroke**-prone spontaneously hypertensive rats.
AUTHOR: Sekiguchi Fumiko; Nakahira Tomohiro; Kawata Kyoko; Sunano Satoru
CORPORATE SOURCE: Department of Anatomy and Physiology, Faculty of Pharmaceutical Sciences, Kinki University, Osaka, Japan.
SOURCE: Clinical and experimental pharmacology & physiology, (2002 Dec) 29 (12) 1066-74.
Journal code: 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20021023
Last Updated on STN: 20030423
Entered Medline: 20030422

AB 1. Responses to endothelium-derived **nitric oxide** (EDNO), indomethacin-sensitive endothelium-derived contracting factor (EDCF) and hyperpolarization by endothelium-derived hyperpolarizing factor (EDHF) and the interaction among these factors in mesenteric arteries from 16-week-old Wistar Kyoto (WKY) rats and age-matched **stroke**-prone spontaneously hypertensive rats (SHRSP) were studied, observing the time-course of the response to 10-5 mol/L acetylcholine (ACh). 2. The effects of EDNO, EDCF and EDHF were blocked by Nomega-nitro-**l-arginine** (10-4 mol/L), indomethacin (10-5 mol/L) and a combination of apamin (5 x 10-6 mol/L) and charybdotoxin (10-7 mol/L), respectively. 3. The response to EDNO observed in the absence of EDCF and EDHF was not

different between preparations from WKY rats and SHRSP. The response to EDCF observed in the absence of EDNO and EDHF was slightly greater in preparations from SHRSP. The response to EDHF in the absence of EDNO and EDCF was much greater in preparations from WKY rats. 4. Endothelium-derived contracting factor attenuated the relaxation in response to EDNO, the attenuation being greater in preparations from SHRSP. Relaxation in response to EDNO was blocked by EDHF in preparations from WKY rats, but not in preparations from SHRSP. 5. The response to EDCF was **augmented** by both EDNO and EDHF. The **augmentation** was greater in preparations from SHRSP. 6. The response to EDHF was attenuated by EDNO in preparations from WKY rats, but not in preparations from SHRSP. The response to EDHF was attenuated by EDCF in preparations from both WKY rats and SHRSP, the attenuation being greater in preparations from SHRSP. 7. These results suggest that there are interactions among these factors in terms of their release or the response to ACh in mesenteric arteries that differ between preparations from WKY rats and SHRSP. In addition, involvement of factors other than these three factors, which also differs between preparations from WKY rats and SHRSP, is suggested.

L20 ANSWER 7 OF 21 MEDLINE on STN
ACCESSION NUMBER: 2002168602 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11900336
TITLE: L-NAME enhances microcirculatory congestion and cardiomyocyte apoptosis during myocardial ischemia-reperfusion in rats.
AUTHOR: Liu Peitan; Xu Baohuan; Forman Lloyd J; Carsia Rocco; Hock Carl E
CORPORATE SOURCE: Department of Cell Biology, University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine, Stratford 08084, USA.
CONTRACT NUMBER: AG00925-03 (NIA)
SOURCE: Shock (Augusta, Ga.), (2002 Mar) 17 (3) 185-92. Journal code: 9421564. ISSN: 1073-2322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020320
Last Updated on STN: 20021003
Entered Medline: 20021002

AB Besides necrosis, apoptosis is the other major mode of cardiomyocyte loss in ischemic cardiovascular disease. In the present study, we examined the hypothesis that **nitric oxide** (NO) protects myocardial function by improving myocardial microcirculation and attenuating cardiomyocyte apoptosis in a rat model of myocardial ischemia/reperfusion (MI/R). The left main coronary artery of anesthetized male rats was ligated for 40 min, followed by 4 h reperfusion. Four groups of animals were studied: sham operated control + saline; sham operated control + N(W)-nitro-**L-arginine** methyl ester (L-NAME); MI/R + saline; MI/R + L-NAME (10 mg/kg, iv, 10 min prior to reperfusion). Results show that MI/R caused a decrease in mean arterial blood pressure (MABP), cardiac index (CI), and **stroke** volume index (SVI). Inhibition of NO synthesis by L-NAME attenuated plasma NO levels, but increased MABP and SVR in sham control rats and rats subjected to MI/R, and further depressed left ventricular function in rats subjected to MI/R as indicated by decreased CI and SVI. Furthermore, administration of L-NAME to rats subjected to MI/R enhanced cardiomyocyte apoptosis as indicated by a significant increase in DNA fragmentation compared to rats

with MI/R alone. Histological study revealed that L-NAME caused arterial constriction and congestion of red blood cells in arteries and capillaries in the peri-ischemic areas of the hearts in rats subjected to MI/R and, interestingly, also in the sham control rats. Data suggest that the mechanism of increased reperfusion injury may be attributable to a "no-reflow" phenomenon induced by L-NAME, resulting in increased cardiomyocyte apoptosis secondary to ischemia and enhanced cytochrome-c release from mitochondria. In addition, cardiac injury may be increased due to the **augmented** oxygen consumption of cardiomyocytes caused by the increased SVR and afterload. These results suggest that endogenous NO may act to improve myocardial microvascular perfusion, reduce SVR, and limit cardiomyocyte apoptosis, thereby, attenuating myocardial dysfunction induced by MI/R.

L20 ANSWER 8 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:109002 BIOSIS
DOCUMENT NUMBER: PREV200300109002
TITLE: Hemodynamic Effects of Co-Administration of **L-Arginine** and Sildenafil (Viagra) in Awake Volunteers.
AUTHOR(S): Tom, Wynnis L. [Reprint Author]; Salahieh, Ali [Reprint Author]; Wallace, Arthur W. [Reprint Author]
CORPORATE SOURCE: Dept. of Anesthesia, Univ. of California, San Francisco, San Francisco, CA, USA
SOURCE: Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2002) No. 2001, pp. Abstract No. A-157. http://www.asa-abstracts.com. cd-rom.
Meeting Info.: 2001 Annual Meeting of the American Society of Anesthesiologists. New Orleans, LA, USA. October 13-17, 2001. American Society of Anesthesiologists Inc.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 2003
Last Updated on STN: 26 Feb 2003

AB Introduction: **L-Arginine** (L-ARG), the precursor for **nitric oxide**, causes vasodilation and improves endothelial function in patients with atherosclerosis. Systemic infusions of **L-arginine** to patients after weaning from coronary artery bypass selectively dilated the coronary vasculature without systemic vascular effects.1 Unfortunately, the dose of **L-arginine** in many studies has been high, with levels approaching 10-2 molar. In-vitro experiments have demonstrated that type V **phosphodiesterase inhibitors** (sildenafil and zaprinast) act synergistically with **L-arginine** to dilate porcine internal mammary arteries.2 In-vivo experiments in pigs demonstrated that combinations of sildenafil and L-ARG result in significant coronary vasodilation and increases in coronary blood flow with minimal systemic hemodynamic effects. This experiment tested the hemodynamic effects of the co-administration of **L-arginine** and sildenafil in awake volunteers. Methods: After Committee on Human Research approval and informed consent, twelve male volunteers at least 45 years of age were studied on three separate days using three randomly selected protocols. Protocol 1: one hour baseline period, oral sildenafil (100 mg PO) administration, one hour later a bolus (30 grams) and infusion (1 mg/kg/min) of **L-arginine** was begun and continued for 2 hours, followed by a recovery period. Protocol 2: one hour baseline period, a bolus and infusion of **L-arginine**, one hour later oral sildenafil administration, then a recovery period. Protocol 3: one hour baseline period, oral **L-arginine**, one hour

later oral sildenafil, then a recovery period. Exclusion criteria included: 1) Unable to give informed consent. 2) Patients with left bundle branch block or pacemaker dependence precluding Holter ST evaluation. 3) Coronary artery disease, **stroke**, congestive heart failure, unstable angina, life threatening arrythmia, aortic stenosis, or Creatinine > 2.0. 4) Use of nitrates. 5) Use of P450 3A4 inhibitors (erythromycin). 6) Hypotension as defined by BP < 90/50 or Hypertension as defined by BP > 170/110. 7) Retinitis Pigmentosa. 8) Use of protease inhibitors. 9) HIV, Hepatitis B or C positivity. Arterial blood pressure, ECG, oxygen saturation, and local vasodilation were recorded continuously by computer. **L-arginine** and L-citrulline levels were measured each hour. Results: There was minimal hemodynamic effect with i.v. infusion or oral administration of **L-arginine** (i.v. L-ARG : change of -2.8 +- 2.6 mmHg, p = NS; oral L-ARG: change of 0.67 +- 2.9 mmHg, p = NS). There was a small decrease in mean arterial blood pressure in response to oral administration of sildenafil (change of -6.6 +- 1.5 mmHg, p = 0.001). There was minimal decrease in blood pressure in response to the combination of sildenafil and either oral or intravenous **L-arginine** (p = NS). L-ARG **augmented** local vasodilation (p < 0.05). The combination of L-ARG and sildenafil had a greater effect on local vasodilation than either alone (p < 0.05). Discussion: Oral and intravenous administration of **L-arginine** hydrochloride is safe. Each has minimal hemodynamic effects. The co-administration of **L-arginine** hydrochloride, oral and intravenous, with sildenafil (100 mg PO) is safe with minimal systemic hemodynamic effects but synergistic local vasodilation.

L20 ANSWER 9 OF 21 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001380298 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11436982
TITLE: Difference in effects of stretch on depressive effect of endothelium-derived **nitric oxide** on noradrenaline- and high-K+-induced contractions between the aortae from normotensive and spontaneously hypertensive rats.
AUTHOR: Sekiguchi F; Miyake Y; Nakazumi S; Shimamura K; Yamamoto K; Sunano S
CORPORATE SOURCE: Department of Anatomy and Physiology, Faculty of Pharmaceutical Sciences, Kinki University, Higashi-Osaka, Osaka, Japan.. fumiko@phar.kindai.ac.jp
SOURCE: Journal of smooth muscle research = Nihon Heikatsukin Gakkai kikanshi, (2001 Feb) 37 (1) 9-23. Journal code: 9211664. ISSN: 0916-8737.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20011105
Entered Medline: 20011101

AB Difference in effects of stretch tension on endothelium-derived **nitric oxide** (EDNO)-dependent depression of noradrenaline (NA)- and high-K+-induced contraction between the aortae from normotensive Wistar Kyoto rats (WKY) a nd **stroke** -pronespontaneously hypertensive rats (SHRSP) was studied. NA-induced contraction in preparations both from WKY and SHRSP was **augmented** in the presence of N(omega)-nitro-**L-arginine** (L-NNA). This **augmentation** was minimized when the spontaneous tone, which

was more prominent in preparations from SHRSP, was subtracted and the effects of L-NNA became less prominent in preparations from SHRSP. The effects of L-NNA were maximal at the stretch tension of 15 mN and, then, decreased as stretch tension increased in both preparations when the spontaneous tone was subtracted. The effects of L-NNA were less prominent when the contraction was initiated by high-K+, although the effects of stretch on high-K+-induced contraction were similar to that of NA-induced contraction. These results suggested 1) that both NA- and high-K+-induced contractions are depressed by EDNO, 2) that the release of EDNO induced by high-K+ is less than that by NA, 3) that increase in stretch tension decreases the release of EDNO, and 4) that the depressive effect of EDNO on contraction is impaired in the aorta of SHRSP.

L20 ANSWER 10 OF 21 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2000213333 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10748273
TITLE: Unaltered endothelium-dependent modulation of contraction in the pulmonary artery of hypertensive rats.
AUTHOR: Matsuda K; Sekiguchi F; Yamamoto K; Shimamura K; Sunano S
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashi-Osaka, Osaka, Japan.
SOURCE: European journal of pharmacology, (2000 Mar 24) 392 (1-2) 61-70.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511

AB Involvement of endothelium-derived **nitric oxide** (EDNO) in alpha-adrenoceptor agonist-induced contractile responses was studied in isolated pulmonary arteries from Wistar Kyoto rats (WKY) and **stroke**-prone spontaneously hypertensive rats (SHRSP). In the presence of propranolol, noradrenaline-induced contraction was potentiated by endothelium removal or by N(G)-nitro-**L-arginine** (L-NOARG). The magnitude of the potentiation was independent of the noradrenaline concentration. L-NOARG also shifted the concentration-response curves for phenylephrine and methoxamine to the left and upward. Contractile responses to 2-amino-5,6,7,8, -tetrahydro-6-ethyl-4H-oxazolo-(5,4-d)-azepine-dihydrochloride (BHT-933) and 5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline (UK-14304) were **augmented** by L-NOARG in a concentration-dependent manner. There were no differences in the effects of L-NOARG on the contractile responses to alpha-adrenoceptor agonists between the preparations from WKY and SHRSP. Endothelium-dependent relaxation in response to acetylcholine was not impaired in the preparations from SHRSP when compared with those from WKY. These observations suggest that the contractile responses to the alpha(1)-adrenoceptor agonists were depressed mainly by basally released EDNO, while the responses to the alpha(2)-adrenoceptor agonists were depressed mainly by EDNO released in response to alpha(2)-adrenoceptor stimulation. The comparable influence of the endothelium on the alpha-adrenoceptor agonist-induced contractions in the pulmonary arteries from WKY and SHRSP, which were markedly different from other arteries, could be explained by the unaltered endothelium-dependent relaxation in the preparations from SHRSP.

L20 ANSWER 11 OF 21 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 1998264253 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9603114
TITLE: Effects of L-NMMA and fluid loading on TNF-induced cardiovascular dysfunction in dogs.
AUTHOR: Quezado Z M; Karzai W; Danner R L; Freeman B D; Yan L; Eichacker P Q; Banks S M; Cobb J P; Cunnion R E; Quezado M J; Sevransky J E; Natanson C
CORPORATE SOURCE: Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: American journal of respiratory and critical care medicine, (1998 May) 157 (5 Pt 1) 1397-405.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980616

AB We investigated the effects of N(omega)-monomethyl-**L-arginine** (L-NMMA) and fluid loading on tumor necrosis factor (TNF)-induced cardiovascular dysfunction in awake dogs. L-NMMA (40 mg x kg(-1) given intravenously over a period of 10 min, and followed by dosing at 40 mg x kg(-1) x h(-1) for 6 h) and TNF (20 or 45 microg x kg(-1) given intravenously for 20 min), given alone or in combination, significantly decreased **stroke** volume, cardiac index, oxygen delivery, and left-ventricular (LV) function plots over a period of 6 h. Of note was that the cardiac-depressant effects of TNF and L-NMMA given together were significantly less than additive. Thus, the combination was beneficial (or significantly less harmful to cardiac performance than expected), possibly because L-NMMA **augmented** cardiac preload as shown by significant increases in both pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP). Fluid challenges at 6 h (Ringer's solution at 80 ml x kg(-1) given over a period of 30 min) also significantly increased PCWP and CVP, and abolished the beneficial preload effect of L-NMMA on cardiac performance. Thus, after fluid loading, the cardiac-depressant effects of TNF and L-NMMA given together became equal to the sum of those produced by TNF and L-NMMA given separately. Although L-NMMA significantly decreased serum nitrite/nitrate levels, TNF did not increase these end products of **nitric oxide** (NO) production relative to controls. Therefore, after preload abnormalities were eliminated with fluid loading, L-NMMA had no beneficial effect on TNF-induced cardiac depression, and TNF did not increase end products of NO production. These findings are not consistent with NO being the mechanism of TNF-induced acute cardiac depression.

L20 ANSWER 12 OF 21 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999109719 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9893721
TITLE: Increased aortic blood pressure contributes to potentiated dobutamine inotropic responses after systemic NO synthase inhibition in sheep.
AUTHOR: Penny D J; Chen H; Smolich J J
CORPORATE SOURCE: Institute of Reproduction and Development, Monash University, Clayton, Victoria, Australia.
SOURCE: Cardiovascular research, (1998 Nov) 40 (2) 282-9.
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210

AB OBJECTIVE: To determine whether inotropic responses to the beta-adrenergic agonist dobutamine are potentiated by systemic inhibition of **nitric oxide** synthase (NOS) with the **L-arginine** analogue N omega-nitro-**L-arginine** (L-NNA), and to establish to what extent any observed responses are related to the increase in aortic blood pressure accompanying systemic NOS inhibition. METHODS: Dobutamine was infused incrementally at rates of 1, 2.5, 5 and 10 micrograms/kg/min in 15 open-chest, anaesthetised ewes before and after inhibition of NO synthesis with i.v. L-NNA (n = 8), or elevation of mean aortic blood pressure to the same extent as attained with NOS inhibition using proximal arterial occlusion (n = 7). RESULTS: By the peak infusion rate, dobutamine increased the maximal rate of rise of left ventricular pressure (LV dP/dtMAX) by 100% ($p < 0.001$) and reduced LV **stroke** work by 18% ($p < 0.01$). L-NNA and arterial occlusion increased resting mean aortic blood pressure by 55 +/- 4 and 51 +/- 3 mmHg respectively. Compared to dobutamine alone, subsequent peak dobutamine-related increases in LV dP/dtMAX were **augmented** by 76% after L-NNA and by 88% after arterial occlusion (both $p < 0.001$). Moreover, dobutamine increased LV **stroke** work by 23% at infusion rates of 1-5 micrograms/kg/min ($p < 0.001$) after L-NNA, and by 17% at an infusion rate of 1 microgram/kg/min ($p < 0.01$) after arterial occlusion. CONCLUSIONS: Systemic NOS inhibition potentiates the effects of dobutamine on LV isovolumic and pumping performance in the intact circulation, but this potentiation is in large part related to the increase in arterial blood pressure accompanying NOS inhibition.

L20 ANSWER 13 OF 21 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998065828 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9403570
TITLE: Regional renal **nitric oxide** release in **stroke**-prone spontaneously hypertensive rats.
AUTHOR: Zuckerman A; Chander P N; Zeballos G A; Stier C T Jr
CORPORATE SOURCE: Department of Pediatrics, New York Medical College, Valhalla 10595, USA.
CONTRACT NUMBER: HL-35522 (NHLBI)
SOURCE: Hypertension, (1997 Dec) 30 (6) 1479-86.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19980108

AB Diminished **nitric oxide** (NO) production has been implicated in the pathogenesis of salt-sensitive hypertension. We questioned whether such a defect is responsible for the malignant hypertension and nephrosclerosis in **stroke**-prone spontaneously hypertensive rats (SHRSP) fed a high-salt/**stroke**-prone diet (S) versus a regular diet (R). NO release from 30-minute incubates of cortex and outer and inner medulla were studied in SHRSP at 10, 12, and 16 weeks of age on the S diet versus R diet. SHRSP-S (n=16) exhibited a marked

age-dependent increase in NO release, especially in the cortex. Increases were only modest in SHRSP-R (n=21). At 16 weeks, cortical NO was 93+/-25 versus 6+/-1 pmol/mg tissue in SHRSP-S versus SHRSP-R (P<.001). Immunohistochemical staining increased mostly for neuronal, slightly for endothelial, and negligibly for inducible isoforms of NO synthase and was predominantly in the cortex of SHRSP-S versus SHRSP-R. Despite similar hypertension in SHRSP-S versus SHRSP-R (mean arterial pressure, 174+/-7 versus 177+/-2 mm Hg), malignant nephrosclerosis was seen only in SHRSP-S, affecting 22+/-6% of glomeruli and 23+/-4 vessels per 100 glomeruli by 16 weeks. N omega-nitro-**L-arginine** (15 mg/kg per day) in SHRSP-S (n=6) abrogated the increase in cortical NO but further **augmented** the hypertension and accelerated lesion development. Wistar-Kyoto rats at 16 weeks on the R diet (n=8) had NO levels similar to those of SHRSP-R, showed increased cortical NO to only 28+/-10 pmol/mg on the S diet (n=9) (P<.05 versus SHRSP-S), but remained normotensive and lesion-free. We conclude that hypertension and lesion development in SHRSP are not due to deficient renal NO. Accelerated onset of malignant nephrosclerosis by NO synthase inhibition suggests that NO is protective in these animals, mitigating the effects of hypertension and S diet on renal pathology.

L20 ANSWER 14 OF 21 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 97390334 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9249238
TITLE: Role of **nitric oxide** in the contractile response to 5-hydroxytryptamine of the basilar artery from Wistar Kyoto and **stroke**-prone rats.
AUTHOR: Salomone S; Morel N; Godfraind T
CORPORATE SOURCE: Laboratoire de Pharmacologie, Universite Catholique de Louvain, Brussels, Belgium.
SOURCE: British journal of pharmacology, (1997 Jul) 121 (6) 1051-8. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971021
Last Updated on STN: 19971021
Entered Medline: 19971008

AB 1. Isolated basilar arteries from spontaneously hypertensive **stroke**-prone rats (SHRSP) are more sensitive to the contractile effect of 5-hydroxytryptamine (5-HT) than those from normotensive Wistar Kyoto rats (WKY). This has been attributed to a different proportion of 5-HT receptor subtypes mediating these responses. In the present study we have examined if differences in **nitric oxide** release could also contribute to this difference in sensitivity to 5-HT. 2. At rest, the normalized internal diameter was significantly smaller in SHRSP (297.4 +/- 3.5 microm, n = 88) than in WKY (375.1 +/- 4.0 microm, n = 62, P<0.01) arteries. The contractile response to 100 mM KCl was higher in WKY (3.57 +/- 0.15 mN mm(-1), n = 22) than in SHRSP arteries (2.32 +/- 0.20 mN mm(-1), n = 28, P<0.01). 3. When added on the plateau of contraction to 5-HT (1 microM), acetylcholine (ACh, 3 microM) evoked significant relaxation in all preparations from WKY (n = 20), but only in 15 out of 26 preparations from SHRSP. The mean relaxations were 55.4 +/- 5.2% in WKY and 20.6 +/- 4.6% in SHRSP (as % of the contractile tone evoked by 5-HT: P<0.01). 4. The NO synthase inhibitor N(omega)-nitro-**L-arginine** (L-NOARG, 0.1 mM) produced a similar increase in tone in both WKY and SHRSP. This tone was equal (in % of the contractile response to 100 mM KCl) to 70.8 +/- 4.4% in WKY (n = 20) and

67.6 +/- 5.9% in SHRSP (n=26) and was reversed by **L-arginine** (1 mM) and by 1,4-dihydropyridine calcium channel blockers (10 nM nisoldipine, 10 nM lacidipine, 100 nM nifedipine). The L-NOARG-induced tone was absent when the arteries were bathed in phosphate-free Krebs (pH 7.4). 5. EC50 values of 5-HT were about four fold smaller in SHRSP than in WKY arteries (P<0.01). The maximal response to 5-HT (Emax) was higher than 100 mM KCl-contraction in SHRSP but not in WKY arteries. Removal of endothelium produced a shift to the left of the 5-HT curve in WKY, but not in SHRSP arteries. 6. When evoked in phosphate-free Krebs, the contractile responses to 5-HT showed tachyphylaxis, but the responses were reproducible by adding the agonist at 30 min intervals. In such conditions, EC50 values of 5-HT were about two fold smaller in SHRSP than in WKY arteries (P<0.01). In phosphate-free Krebs, the blockade of NO synthase did not change the contractile response to 100 mM KCl; it reduced EC50 and increased Emax of 5-HT in WKY, but not in SHRSP. 7. These results confirm that the sensitivity to 5-HT is higher in basilar artery isolated from SHRSP than in those from WKY. They show that endothelium-dependent vasorelaxation to ACh is impaired in SHRSP. The finding that removal of endothelium or blockade of NO synthase **augmented** the contractile response to 5-HT in WKY, but not in SHRSP basilar arteries indicates that the difference in responsiveness to 5-HT observed between WKY and SHRSP basilar arteries might be, at least in part, related to dissimilarities in NO release. Furthermore, the L-NOARG-induced contraction sensitive to calcium channel blockers indicates that, in basilar arteries, NO production might lower L-type calcium channel opening and thereby control the tone of the vessels.

L20 ANSWER 15 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97304803 EMBASE
DOCUMENT NUMBER: 1997304803
TITLE: Pathophysiology of cerebral injury and future management.
AUTHOR: Baumgartner W.A.; Redmond M.; Brock M.; Tseng E.; Blue M.E.; Troncoso J.C.; Johnston M.V.; Bonser R.S.; Griepp R.B.; Westaby S.; Heafield T.; Wolner
CORPORATE SOURCE: Dr. W.A. Baumgartner, Johns Hopkins Hospital, 600 N. Wolfe Wolfe, Baltimore, MD 21287-4618, United States
SOURCE: Journal of Cardiac Surgery, (1997) Vol. 12, No. 2 SUPPL., pp. 300-311. .
Refs: 38
ISSN: 0886-0440 CODEN: JCASE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
009 Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 971030
Last Updated on STN: 971030

AB Central nervous system dysfunction continues to represent significant morbidity and associated mortality in patients undergoing cardiac surgery. Neurological dysfunction is most exaggerated in patients undergoing hypothermic circulatory arrest (HCA). Although surgical techniques, anesthetic management, and postoperative care have significantly improved over the past two decades, the incidence of **stroke** and other neurocognitive deficits remains problematic. Understanding the mechanisms of cell death associated with HCA may provide information that is germane

to all types of cerebral injury involved in cardiac surgery. Using a closed-chest cardiopulmonary bypass model, dogs underwent 2 hours of circulatory arrest at 18°C followed by resuscitation and recovery for 3 days. Animals were assessed functionally by a species-specific behavioral scale, histologically for patterns of selective neuronal necrosis and receptor autoradiography for NMDA glutamate receptor subtype expression. Using a selective NMDA (- glutamate) receptor antagonist (MK801), an AMPA-antagonist (NBQX) and a nonspecific neuroprotectant (GM1-ganglioside), the role of glutamate excitotoxicity in the development of HCA-induced brain injury was documented and validated. Using a similar canine preparation, a microdialysis technique was used to evaluate the role of **nitric oxide** in neuronal death. Arginine plus oxygen is converted to **nitric oxide** plus citrulline by the action of **nitric oxide** synthase. Simultaneous infusion of artificial cerebrospinal fluid containing L-[14C] arginine or L-[14C] arginine and L-NAME (a **nitric oxide** synthase inhibitor) was performed in contralateral hemispheres. Citrulline recovery in the cerebrospinal fluid, citrulline production in vitro from canine cortical homogenates, and **nitric oxide** metabolites in the serum were all significantly increased during HCA and reperfusion. These studies demonstrated that neurotoxicity following HCA involves a significant and early induction of neuronal NOS expression and neuronal processes leading to widespread **augmented** NO production in the brain. Continued research into the pathophysiologic mechanisms involved in cerebral injury will undoubtedly yield a safe and reliable neuroprotectant strategy.

L20 ANSWER 16 OF 21 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 97277942 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9131293
TITLE: Tissue variation of acute haemodynamic changes by NG-nitro-**L-arginine** in **stroke**-prone spontaneously hypertensive and Wistar-Kyoto rats.
AUTHOR: Higashino H; Simeonova K; Lambev I; Suzuki A
CORPORATE SOURCE: Department of Pharmacology, Kinki University School of Medicine, Osaka, Japan.. higasino@med.kindai.ac.jp
SOURCE: Clinical and experimental pharmacology & physiology, (1997 Mar-Apr) 24 (3-4) 249-55.
Journal code: 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 19970709
Entered Medline: 19970624

AB 1. The acute effects of **nitric oxide** synthase inhibition on the haemodynamics in **stroke**-prone spontaneously hypertensive (SHRSP) and normotensive Wistar-Kyoto (WKY) rats were investigated using radiolabelled microspheres. 2. Intravenous administration of 3 and 6 mg/kg NG-nitro-**L-arginine** (L-NNA) caused a significant increase in total peripheral resistance, a decrease in cardiac output and an increase in blood pressure in both SHRSP and WKY rats. 3. Significant decreases in regional blood flow (RBF) in the lung, muscle and stomach of WKY rats were observed following L-NNA administration. 4. NG-nitro-**L-arginine** produced a 70% increase in brain regional blood flow at a dose of 6 mg/kg only in SHRSP. 5. There was a variation in the involvement of **nitric oxide** (NO) in different tissues. 6. It is concluded that

hypertension in SHRSP **augments** NO-mediated vasodilation.

L20 ANSWER 17 OF 21 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 95205859 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7898083
TITLE: Endothelial dysfunction in aorta of the spontaneously hypertensive, **stroke**-prone rat: effects of therapy with verapamil and trandolapril alone and in combination.
AUTHOR: Novosel D; Lang M G; Noll G; Luscher T F
CORPORATE SOURCE: Department of Medicine, University Hospitals Basel, Switzerland.
SOURCE: Journal of cardiovascular pharmacology, (1994 Dec) 24 (6) 979-85.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950504
Last Updated on STN: 19950504
Entered Medline: 19950424

AB The effects of chronic therapy with the angiotensin-converting enzyme (ACE) inhibitor trandolapril and/or Ca2+ antagonist verapamil on endothelial and vascular smooth muscle (VSM) function were studied in spontaneously hypertensive, **stroke**-prone rats (SHRSP). Dosages decreasing systolic blood pressure (SBP) by 20% were administered orally (p.o.) by gavage as monotherapy or combination therapy for 8 weeks, beginning at age 6 weeks. Combination therapy dosages were the same as those used in monotherapy (trandolapril 0.7 mg/kg/day verapamil 20 mg/kg/day) in one group; the second group received only half the monotherapy dosage. The study was placebo-controlled and performed in parallel groups. Isometric tension was measured in aortic rings suspended in organ chambers (95% C2/5% CO2; 37 degrees C). SBP decreased in all groups, as compared with placebo [30-47 mm Hg, analysis of variance (ANOVA), $p < 0.05$], but decrease was more pronounced in rats receiving high-dose combination (76 mm Hg, ANOVA, $p < 0.05$). In norepinephrine (NE)-contracted rings, endothelium-dependent relaxation to acetylcholine (ACh) was **augmented** similarly with all forms of therapy (maximal relaxations 89-94%) as compared with placebo (64 +/- 6%, $p < 0.05$). In contrast, the response to sodium nitroprusside (SNP) was similar in all groups (NS). In quiescent rings, ACh elicited endothelium-dependent contractions (in the presence of N omega-monomethyl-**L-arginine**, L-NAME) that were not affected by therapy.(ABSTRACT TRUNCATED AT 250 WORDS)

L20 ANSWER 18 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:120507 BIOSIS
DOCUMENT NUMBER: PREV199598134807
TITLE: Endothelium-dependent contractions induced by acetylcholine in renal arteries isolated from WKY and SHRSP.
AUTHOR(S): Nishimura, Yoshitaka; Suzuki, Aritomo; Miyatake, Rie; Nakai, Yoshihiro; Koh, Tosei
CORPORATE SOURCE: Dep. Pharmacol., Kinki University Sch. Med., Osaka, Japan
SOURCE: Medical Journal of Kinki University, (1994) Vol. 19, No. 4 SUPPL., pp. 35-38.
CODEN: KDIZDD. ISSN: 0385-8367.
DOCUMENT TYPE: Article

LANGUAGE: Japanese
ENTRY DATE: Entered STN: 29 Mar 1995
Last Updated on STN: 29 Mar 1995

AB We examined the contractile responses to acetylcholine (ACh) in isolated renal artery rings obtained from WKY and SHRSP at 3 and 6 months of age. ACh caused a transient contraction in endothelium-intact renal arteries from WKY and SHRSP. ACh-induced contraction was abolished by removal of the endothelium, and was **augmented** by pretreatment with N-G-nitro-**L-arginine** (NOARG) in both groups. Indomethacin completely inhibited ACh-induced contraction in NOARG-treated arteries of WKY and SHRSP. Contraction induced by ACh was significantly smaller in SHRSP at 3 and 6 months of age than in age-matched WKY. ACh-induced endothelium-dependent relaxation in renal arteries precontracted with phenylephrine was decreased in SHRSP at 3 and 6 months of age when compared to age-matched WKY. Relaxation induced by ACh was inhibited by NOARG in both groups. These results suggest that ACh produces both contractile responses mediated by cyclooxygenase products and relaxation responses mediated by **nitric oxide** in an endothelium-dependent manner, and that these responses were impaired in SHRSP.

L20 ANSWER 19 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:474915 BIOSIS
DOCUMENT NUMBER: PREV199396108515
TITLE: Involvement of **nitric oxide** and prostaglandins in gastric mucosal hyperemia of portal-hypertensive anesthetized rats.
AUTHOR(S): Casadevall, Maria; Panes, Julian; Pique, Josep M. [Reprint author]; Marroni, Norma; Bosch, Jaume; Whittle, Brendan J. R.
CORPORATE SOURCE: Gastroenterol. Dep., Hosp. Clin., Villarroel 170, 08036 Barcelona, Spain
SOURCE: Hepatology, (1993) Vol. 18, No. 3, pp. 628-634. CODEN: HPTLD9. ISSN: 0270-9139.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Oct 1993
Last Updated on STN: 3 Jan 1995

AB This study investigates the effects of inhibition of **nitric oxide** synthesis by N-G-nitro-**L-arginine** methyl ester (L-NAAIE), the inhibition of prostaglandin synthesis with indomethacin and the combined effects on gastric mucosal hyperemia of ketamine-anesthetized rats with portal hypertension induced by partial portal vein ligation. The hydrogen gas-clearance technique was used for measurement of gastric mucosal blood flow. Blood pressure increased with L-NAME administration in a similar manner in portal-hypertensive and sham-operated rats. Low doses of L-NAME (1 and 3 mg/kg, intravenously) caused a significant and dose-dependent reduction in gastric mucosal blood flow in portal-hypertensive rats but had no effect on sham-operated animals. With a higher dose of L-NAME (13 mg/kg, intravenously), a significant decrease in gastric mucosal blood flow was observed in both portal-hypertensive and sham-operated rats. Indomethacin pretreatment (5 mg/kg, subcutaneously) caused a significant decrease in basal gastric mucosal blood flow of portal-hypertensive rats but did not modify this parameter in sham-operated animals. In sham-operated rats pretreated with indomethacin, the lower dose of L-NAME (3 mg/kg) did not significantly modify basal gastric mucosal blood flow. Likewise, pretreatment with indomethacin in sham-operated rats did not **augment** the significant reduction in gastric mucosal blood flow produced by the higher

dose of L-NAME. In portal-hypertensive rats the significant dose-dependent reduction in gastric mucosal blood flow induced by L-NAME (3 and 13 mg/kg) was not significantly altered by pretreatment with indomethacin. Portal pressure was higher in portal-hypertensive than in sham-operated rats, and no significant differences were observed in this parameter between portal-hypertensive animals treated with different doses of L-NAME. These results indicate that both **nitric oxide** and prostaglandins may be involved in the gastric mucosal hyperemia of portal-hypertensive rats. However, no synergistic interactions between these two endogenous vasodilators could be observed in this experimental model.

L20 ANSWER 20 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 12

ACCESSION NUMBER: 1994:222129 BIOSIS
DOCUMENT NUMBER: PREV199497235129
TITLE: Modulation of contraction of aortic smooth muscle by endothelium and its decrease in spontaneously hypertensive rats.
AUTHOR(S): Sunano, Satoru; Kaneko, Kyoko; Yamamoto, Kazuo; Sasaki, Fumiko
CORPORATE SOURCE: Res. Inst. Hypertension, Kinki Univ., Osaka, Japan
SOURCE: Medical Journal of Kinki University, (1993) Vol. 18, No. 4 SUPPL., pp. 65-67.
CODEN: KDIZDD. ISSN: 0385-8367.
DOCUMENT TYPE: Article
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 24 May 1994
Last Updated on STN: 25 May 1994

AB Noradrenaline-induced contraction was potentiated by the removal of endothelium and the potentiation was greater in the aorta of Wistar Kyoto (WKY) rats than in that of **stroke**-prone spontaneously hypertensive rats (SHRSP). N-G-nitro-**L-arginine** (L-NNA, 100 mu-M), which inhibits **nitric oxide** (NO) synthesis, also potentiated the noradrenaline-induced contraction in the endothelium-intact preparation. The effect of L-NNA was greater in the WKY preparation. Acetylcholine-induced relaxation in the endothelium-intact aorta was impaired in the SHRSP preparation. Phenylephrine- and clonidine-induced contractions were **augmented** by pretreatment with L-NNA or removal of endothelium. These findings indicate that the vascular endothelium modulates the noradrenaline-induced contraction by releasing NO through alpha-1- and alpha-2-adrenergic receptors. The depression of noradrenaline-induced contraction by the endothelium was **augmented** by the repetition of the initiation of the contraction. The **augmentation** of the depression was less prominent in the SHRSP aorta. This also suggests that the release of NO through these adrenergic receptors is reduced in the aorta of SHRSP.

L20 ANSWER 21 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 13

ACCESSION NUMBER: 1991:140183 BIOSIS
DOCUMENT NUMBER: PREV199191076723; BA91:76723
TITLE: EFFECTS OF N-G NITRO-**L-ARGININE** METHYL ESTER OR INDOMETHACIN ON DIFFERENTIAL REGIONAL AND CARDIAC HEMODYNAMIC ACTIONS OF ARGININE VASOPRESSIN AND LYSINE VASOPRESSIN IN CONSCIOUS RATS.
AUTHOR(S): GARDINER S M [Reprint author]; COMPTON A M; KEMP P A; BENNETT T
CORPORATE SOURCE: DEP PHYSIOL PHARMACOLOGY, NOTTINGHAM UNIV MED SCH, QUEEN'S MED CENTRE, NOTTINGHAM NG7 2UH, UK

SOURCE: British Journal of Pharmacology, (1991) Vol. 102, No. 1, pp. 65-72.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 14 Mar 1991
Last Updated on STN: 22 May 1991

AB Measurements of changes in renal, mesenteric and hindquarters hemodynamics or cardiac haemodynamics in response to i.v. bolus doses of arginine vasopressin (AVP) or lysine vasopressin (LVP, 0.7 and 7.0 pmol) were made in conscious, chronically-instrumented Long Evans rats. In some experiments AVP and LVP were administered during an infusion of NG-nitro-**L-arginine** methyl ester (L-NAME: 1.0 or 0.3 mg kg-1 h-1) to determine whether or not inhibition of **nitric oxide** production influenced the cardiovacular effects of the peptides. In other experiments, indomethacin (bolus dose of 5 mg kg-1 followed by infusion at 5 mg kg-1 h-1) was given to determine the possible involvement of cyclo-oxygenase products in the responses to AVP and LVP. Under control conditions, the lower dose of LVP had significantly greater effects than AVP on heart rate, mean arterial blood pressure, renal, mesenteric and hindquarters conductances, total peripheral conductance, cardiac index, peak aortic flow and +dF/dtmax. The higher dose of LVP had significantly greater effects than AVP on all variables (i.e. including **stroke** index and central venous pressure). In the presence of L-NAME (1 mg kg-1 h-1) there was a sustained increase in mean arterial blood pressure (+ 23 ± 3 mmHg) and reductions in mesenteric (-38 ± 4%) and hindquarters (-30 ± 6%) vascular conductances. Under these conditions the difference in the pressor effects of AVP and LVP was abolished, but their differential effects on regional and cardiac haemodynamics persisted. This dose of L-NAME did not change cardiac baroreflex sensitivity. During infusion of L-NAME at a lower rate (0.3 mg kg-1 h-1), baseline cardiovascular status was unchanged and regional haemodynamic effects of AVP and LVP were enhanced, but the differences in the regional vasocontrictor responses to the two peptides persisted. Indomethacin (5 mg kg-1 bolus, then 5 mg kg-1 h-1 infusion) **augmented** the renal vasoconstrictor responses to AVP and LVP, but abolished the difference in the hindquarters vasoconstrictor responses to the two peptides. However, the differences in the pressor and the renal and mesenteric vasoconstrictor effects of AVP and LVP still occurred in the presence of indomethacin. The results indicate that AVP normally has lesser cardiovascular effects than LVP but this difference does not seem to be due to more effective stimulation of **nitric oxide** -mediated or cyclo-oxygenase-dependent vasodilator mechanisms by AVP than LVP.

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=> d que stat l24
L6            3 SEA FILE=REGISTRY ABB=ON  (DETANONOATE OR PAPANONOATE OR
                S-NITROSO-N-ACETYLPENICILLAMINE OR SODIUM NITROPRUSSIDE OR
                SODIUM NITROGLYCERINE OR PHOSPHODIESTERASE INHIBITORS OR
                L-ARGININE)/CN
L7        76296 SEA FILE=HCAPLUS ABB=ON  L6 OR ?DETANONOATE? OR ?PAPANONOATE?
                OR S(W)?NITROSO?(W)N(W)?ACETYLPENICILLAMIN? OR ?PHOSPHODIESTERA
                S?(W)?INHIBIT? OR L(W)?ARGININE?
L8            1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L9        20263 SEA FILE=HCAPLUS ABB=ON  L7 AND (L8 OR ?NITRIC?(W)?OXID?)
L15        1081 SEA FILE=HCAPLUS ABB=ON  L9 AND (?NEURON?(3A)?GROW? OR
                ?AUGMENT?)
L17          14 SEA FILE=HCAPLUS ABB=ON  L15 AND ?STROKE?
L21         209 SEA FILE=USPATFULL ABB=ON  L17 AND (PRD<19990614 OR PD<19990614
                )
L24          10 SEA FILE=USPATFULL ABB=ON  L21 AND ?DONOR?(W)?COMPOUND?

=> d ibib abs l24 1-10

L24  ANSWER 1 OF 10  USPATFULL on STN
ACCESSION NUMBER:       2006:27455  USPATFULL
TITLE:                  Red blood cells loaded with S-nitrosothiol and uses
                        therefor
INVENTOR(S):            Stamler, Jonathan S., Chapel Hill, NC, UNITED STATES
                        Bonaventura, Joseph, Beaufort, NC, UNITED STATES
                        Pawloski, John R., Raleigh, NC, UNITED STATES
                        McMahon, Timothy J., Durham, NC, UNITED STATES
PATENT ASSIGNEE(S):     Duke University, Durham, NC, UNITED STATES, 27710 (U.S.
                        corporation)

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2006024283      A1   20060202
APPLICATION INFO.:      US 2005-179349     A1   20050712  (11)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2001-45603, filed on 23 Oct
                        2001, GRANTED, Pat. No. US 6916471 Continuation-in-part
                        of Ser. No. US 2000-724305, filed on 28 Nov 2000,
                        ABANDONED Continuation of Ser. No. US 1997-873679,
                        filed on 12 Jun 1997, GRANTED, Pat. No. US 6203789
                        Continuation-in-part of Ser. No. WO 1996-US14664, filed
                        on 13 Sep 1996, PENDING Continuation of Ser. No. US
                        1996-616255, filed on 15 Mar 1996, GRANTED, Pat. No. US
                        6153186

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 1995-3801P      19950915 (60)           <--
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP, 300 S. WACKER
                        DRIVE, 32ND FLOOR, CHICAGO, IL, 60606, US
NUMBER OF CLAIMS:       16
EXEMPLARY CLAIM:        1-8
NUMBER OF DRAWINGS:     24 Drawing Page(s)
LINE COUNT:             2496
AB      Red blood cells can be loaded with low molecular weight nitrosylating
        agents, such as S-nitrosothiols, to act as a delivery system for
        NO.sup.+ groups to tissues. Loaded red blood cells can be used in
        methods of therapy for conditions which are characterized by abnormal
        O.sub.2 metabolism of tissues, oxygen-related toxicity, abnormal
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vascular tone, abnormal red blood cell adhesion, or abnormal O.sub.2 delivery by red blood cells. Such treatment of red blood cells can be extended to in vivo therapies, with the object to achieve an increase in the ratio of red blood cell S-nitrosothiol to hemoglobin.

L24 ANSWER 2 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2005:188863 USPATFULL
TITLE: Method and pharmaceutical composition for inhibiting premature rapture of fetal membranes, ripening of uterine cervix and preterm labor in mammals
INVENTOR(S): Leibovitz, Shamir, Tel Aviv, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005163771	A1	20050728
APPLICATION INFO.:	US 2005-80474	A1	20050316 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-286959, filed on 4 Nov 2002, PENDING Continuation of Ser. No. US 2000-554124, filed on 9 May 2000, ABANDONED A 371 of International Ser. No. WO 1998-IL572, filed on 24 Nov 1998

	NUMBER	DATE	
PRIORITY INFORMATION:	IL 1997-122278	19971124	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Martin Moynihan, c/o Anthony Castorina, Suite 207, 2001 Jefferson Davis Highway, Arlington, VA, 22202, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 2073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and a pharmaceutical composition for inhibiting premature rapture of the fetal membranes, ripening of the uterine cervix and preterm labor of female mammals including human. The method includes the step of administering compounds for reversing at least two biochemical conditions being associated with the above processes. The pharmaceutical composition includes compounds for reversing at least two biochemical conditions being associated with the above processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 3 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2004:126544 USPATFULL
TITLE: Use of inhaled NO as anti-inflammatory agent
INVENTOR(S): Zapol, Warren M., Concord, MA, UNITED STATES
Bloch, Kenneth D., Brookline, MA, UNITED STATES
Rosenzweig, Anthony, Newton, MA, UNITED STATES
PATENT ASSIGNEE(S): The General Hospital Corporation, a Massachusetts corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004096523	A1	20040520
	US 6811768	B2	20041102
APPLICATION INFO.:	US 2003-694490	A1	20031027 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-971003, filed on 14 Nov 1997, GRANTED, Pat. No. US 6656452

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-62926P	19971021 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 450
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for lessening or preventing non-pulmonary ischemia-reperfusion injury or inflammation in a mammal by identifying a mammal which has ischemia-reperfusion or is at risk for developing ischemia-reperfusion in a non-pulmonary tissue; and causing the mammal to inhale a therapeutically effective amount of gaseous **nitric oxide** sufficient to diminish the ability of leukocytes or platelets to become activated in a manner that contributes to an inflammatory process at the site of the ischemia-reperfusion or inflammation in the non-pulmonary tissue, thereby lessening or preventing non-pulmonary ischemia-reperfusion injury in the mammal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 4 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2003:314459 USPATFULL
TITLE: Use of inhaled NO as anti-inflammatory agent
INVENTOR(S): Zapol, Warren M., Concord, MA, United States
Bloch, Kenneth D., Brookline, MA, United States
PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6656452	B1	20031202	
APPLICATION INFO.:	US 1997-971003		19971114	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-62926P	19971021 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Hartley, Michael G.
ASSISTANT EXAMINER: Haghighatian, Mina
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 457
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for lessening or preventing non-pulmonary ischemia-reperfusion injury or inflammation in a mammal by identifying a mammal which has ischemia-reperfusion or is at risk for developing ischemia-reperfusion in a non-pulmonary tissue; and causing the mammal to inhale a therapeutically effective amount of gaseous **nitric oxide** sufficient to diminish the ability of leukocytes or platelets to become activated in a manner that contributes to an inflammatory process at the site of the ischemia-reperfusion or inflammation in the non-pulmonary tissue, thereby lessening or preventing non-pulmonary ischemia-reperfusion injury in the mammal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 5 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2003:165465 USPATFULL
TITLE: Method and pharmaceutical composition for inhibiting premature rapture of fetal membranes, ripening of uterine cervix and preterm labor in mammals
INVENTOR(S): Leibovitz, Shamir, Tel Aviv, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003113319	A1	20030619
APPLICATION INFO.:	US 2002-286959	A1	20021104 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-554124, filed on 9 May 2000, ABANDONED A 371 of International Ser. No. WO 1998-IL572, filed on 24 Nov 1998, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	IL 1997-122278	19971124	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Sol Sheinbein, c/o Anthony Castorina, Suite 207, 2001 Jefferson Davis Highway, Arlington, VA, 22202
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 2073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and a pharmaceutical composition for inhibiting premature rapture of the fetal membranes, ripening of the uterine cervix and preterm labor of female mammals including human. The method includes the step of administering compounds for reversing at least two biochemical conditions being associated with the above processes. The pharmaceutical composition includes compounds for reversing at least two biochemical conditions being associated with the above processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 6 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2003:145907 USPATFULL
TITLE: Method and pharmaceutical composition for inhibiting premature rupture of fetal membranes, ripening of uterine cervix and preterm labor in mammals
INVENTOR(S): Leibovitz, Shamir, Tel Aviv, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003099651	A1	20030529
APPLICATION INFO.:	US 2003-338850	A1	20030109 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-886114, filed on 22 Jun 2001, PENDING Division of Ser. No. US 2000-554124, filed on 9 May 2000, PENDING A 371 of International Ser. No. WO 1998-IL572, filed on 24 Nov 1998, PENDING

	NUMBER	DATE	
PRIORITY INFORMATION:	IL 1997-122278	19971124	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: G.E. EHRLICH (1995) LTD., c/o ANTHONY CASTORINA, SUITE 207, 2001 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2090
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and a pharmaceutical composition for inhibiting premature rupture of the fetal membranes, ripening of the uterine cervix and preterm labor of female mammals including human. The method includes the step of administering compounds for reversing at least two biochemical conditions being associated with the above processes. The pharmaceutical composition includes compounds for reversing at least two biochemical conditions being associated with the above processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 7 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2003:10605 USPATFULL
TITLE: Red blood cells loaded with S-nitrosothiol and uses therefor
INVENTOR(S): Stamler, Jonathan S., Chapel Hill, NC, UNITED STATES
Bonaventura, Joseph, Beaufort, NC, UNITED STATES
Pawloski, John R., Raleigh, NC, UNITED STATES
McMahon, Timothy J., Durham, NC, UNITED STATES
PATENT ASSIGNEE(S): Duke University, Durham, NC, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003008300	A1	20030109	
	US 6916471	B2	20050712	
APPLICATION INFO.:	US 2001-45603	A1	20011023	(10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-724305, filed on 28 Nov 2000, PENDING Continuation of Ser. No. US 1997-873679, filed on 12 Jun 1997, GRANTED, Pat. No. US 6203789 Continuation-in-part of Ser. No. WO 1996-US14664, filed on 13 Sep 1996, UNKNOWN Continuation of Ser. No. US 1996-616255, filed on 15 Mar 1996, GRANTED, Pat. No. US 6153186

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1995-3801P	19950915 (60)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: David E. Brook, Esq., HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA, 01742-9133
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 2601
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Red blood cells can be loaded with low molecular weight nitrosylating agents, such as S-nitrosothiols, to act as a delivery system for NO.sup.+ groups to tissues. Loaded red blood cells can be used in methods of therapy for conditions which are characterized by abnormal O.sub.2 metabolism of tissues, oxygen-related toxicity, abnormal vascular tone, abnormal red blood cell adhesion, or abnormal O.sub.2 delivery by red blood cells. Such treatment of red blood cells can be

extended to in vivo therapies, with the object to achieve an increase in the ratio of red blood cell S-nitrosothiol to hemoglobin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 8 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2002:54354 USPATFULL
TITLE: Method and pharmaceutical composition for inhibiting premature rapture of fetal membranes, ripening of uterine cervix and preterm labor in mammals
INVENTOR(S): Leibovitz, Shamir, Tel Aviv, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002031513	A1	20020314
APPLICATION INFO.:	US 2001-886114	A1	20010622 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-554124, filed on 9 May 2000, PENDING A 371 of International Ser. No. WO 1998-IL572, filed on 24 Nov 1998, UNKNOWN

	NUMBER	DATE	
PRIORITY INFORMATION:	IL 1997-122278	19971124	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SOL SHEINBEIN, c/o ANTHONY CASTORINA, SUITE 207, 2001 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2067
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and a pharmaceutical composition for inhibiting premature rapture of the fetal membranes, ripening of the uterine cervix and preterm labor of female mammals including human. The method includes the step of administering compounds for reversing at least two biochemical conditions being associated with the above processes. The pharmaceutical composition includes compounds for reversing at least two biochemical conditions being associated with the above processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 9 OF 10 USPATFULL on STN
ACCESSION NUMBER: 97:3725 USPATFULL
TITLE: Nitrosylation of protein SH groups and amino acid residues as a therapeutic modality
INVENTOR(S): Stamler, Jonathan, Boston, MA, United States
Loscalzo, Joseph, Dedham, MA, United States
Simon, Daniel, Waban, MA, United States
Singel, David, Arlington, MA, United States
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5593876		19970114	<--
APPLICATION INFO.:	US 1994-287830		19940809 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-198854, filed on 17 Feb 1994 which is a division of Ser. No. US 1992-943835, filed on 14 Sep 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-791668, filed

on 14 Nov 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lilling, Herbert J.
LEGAL REPRESENTATIVE: Herron, Charles J., Olstein, Elliot M.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 51 Drawing Figure(s); 41 Drawing Page(s)
LINE COUNT: 1791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nitrosylation of proteins and amino acid groups enables selective regulation of protein function, and also endows the proteins and amino acids with additional smooth muscle relaxant and platelet inhibitory capabilities. Thus, the invention relates to novel compounds achieved by nitrosylation of protein thiols. Such compounds include: S-nitroso-t-PA, S-nitroso-cathepsin; S-nitroso-lipoprotein; and S-nitroso-immunoglobulin. The invention also relates to therapeutic use of S-nitroso-protein compounds for regulating protein function, cellular metabolism and effecting vasodilation, platelet inhibition, relaxation of non-vascular smooth muscle, and increasing blood oxygen transport by hemoglobin and myoglobin. The compounds are also used to deliver **nitric oxide** in its most bioactive form in order to achieve the effects described above, or for in vitro nitrosylation of molecules present in the body. The invention also relates to the nitrosylation of oxygen, carbon and nitrogen moieties present on proteins and amino acids, and the use thereof to achieve the above physiological effects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 10 OF 10 USPATFULL on STN
ACCESSION NUMBER: 96:62637 USPATFULL
TITLE: Methods and devices for relaxing smooth muscle contractions
INVENTOR(S): Zapol, Warren M., Concord, MA, United States
PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5536241		19960716	<--
APPLICATION INFO.:	US 1993-36522		19930324 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1992-904117, filed on 25 Jun 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-850383, filed on 11 Mar 1992, now patented, Pat. No. US 5396882 And Ser. No. US 1991-767234, filed on 27 Sep 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-622865, filed on 5 Dec 1990, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Green, Randall L.
ASSISTANT EXAMINER: Alexander, V.
LEGAL REPRESENTATIVE: Fish & Richardson
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 808
AB Methods and devices for using **nitric oxide** (NO) to decrease or prevent the contraction of a smooth muscle in a

non-respiratory-tract organ of an animal, the organ being one which contains or is surrounded by a biological fluid which is not blood, which method includes the step of introducing an effective amount of NO into the fluid.

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=> d his ful

     (FILE 'HOME' ENTERED AT 16:30:06 ON 17 FEB 2006)

     FILE 'HCAPLUS' ENTERED AT 16:30:21 ON 17 FEB 2006
                E CHOPP MICHAEL/AU
L1           176 SEA ABB=ON  ("CHOPP M"/AU OR "CHOPP MICHAEL"/AU)
                E ZHANG RUI LAN/AU
L2            29 SEA ABB=ON  ("ZHANG RUI L"/AU OR "ZHANG RUI LAN"/AU)
L3            29 SEA ABB=ON  L1 AND L2
L4             4 SEA ABB=ON  L3 AND ?NITRIC?(W)?OXID?
L5               ANALYZE L4 2-3 CT :       9 TERMS

     FILE 'REGISTRY' ENTERED AT 16:35:38 ON 17 FEB 2006
L6             3 SEA ABB=ON  (DETANONOATE OR PAPANONOATE OR S-NITROSO-N-ACETYLPE
                  NICILLAMINE OR SODIUM NITROPRUSSIDE OR SODIUM NITROGLYCERINE
                  OR PHOSPHODIESTERASE INHIBITORS OR L-ARGININE)/CN
                  E DETANONOATE/CN

     FILE 'HCAPLUS' ENTERED AT 16:37:14 ON 17 FEB 2006
L7         76296 SEA ABB=ON  L6 OR ?DETANONOATE? OR ?PAPANONOATE? OR S(W)?NITROS
                  O?(W)N(W)?ACETYLPENICILLAMIN? OR ?PHOSPHODIESTERAS?(W)?INHIBIT?
                   OR L(W)?ARGININE?

     FILE 'REGISTRY' ENTERED AT 16:39:47 ON 17 FEB 2006
L8             1 SEA ABB=ON  NITRIC OXIDE/CN

     FILE 'HCAPLUS' ENTERED AT 16:39:55 ON 17 FEB 2006
L9         20263 SEA ABB=ON  L7 AND (L8 OR ?NITRIC?(W)?OXID?)
L10           10 SEA ABB=ON  L9 AND ?NEURON?(3A)?GROW?
L11            2 SEA ABB=ON  L9 AND ?POST?(3A)?STROKE?
L12         1072 SEA ABB=ON  L9 AND ?AUGMENT?
L13           14 SEA ABB=ON  L12 AND ?STROKE?
L14          281 SEA ABB=ON  L9 AND ?STROKE?
L15         1081 SEA ABB=ON  L9 AND (?NEURON?(3A)?GROW? OR ?AUGMENT?)
L16            0 SEA ABB=ON  L15 AND (?POST? OR ?FOLLOW?)(3A)?STROKE?
L17           14 SEA ABB=ON  L15 AND ?STROKE?
L18            8 SEA ABB=ON  L17 AND (PRD<19990614 OR PD<19990614) 8 cits from CA Plus

     FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 16:43:33 ON
     17 FEB 2006
L19           45 SEA ABB=ON  L17
L20           21 DUP REMOV L19 (24 DUPLICATES REMOVED) 21 cits from above) d.b.'s

     FILE 'USPATFULL' ENTERED AT 16:44:33 ON 17 FEB 2006
L21          209 SEA ABB=ON  L17 AND (PRD<19990614 OR PD<19990614)
L22            0 SEA ABB=ON  L21 AND ?NITRIC?(W)?ACID?(W)?DONOR?
L23          178 SEA ABB=ON  L21 AND ?DONOR?
L24           10 SEA ABB=ON  L21 AND ?DONOR?(W)?COMPOUND? 10 cits from CA Plus

     FILE HOME

     FILE HCAPLUS

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FILE LAST UPDATED: 16 Feb 2006 (20060216/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 15 FEB 2006 HIGHEST RN 874326-73-5
DICTIONARY FILE UPDATES: 15 FEB 2006 HIGHEST RN 874326-73-5

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Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE MEDLINE
FILE LAST UPDATED: 16 FEB 2006 (20060216/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 will soon be available. For details on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 February 2006 (20060215/ED)

FILE EMBASE
FILE COVERS 1974 TO 9 Feb 2006 (20060209/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE COVERS APR 1973 TO OCTOBER 27, 2005

>>> GRAPHIC IMAGES AVAILABLE <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE. USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION ABOUT THE IPC REFORM <<<

FILE JICST-EPLUS
FILE COVERS 1985 TO 14 FEB 2006 (20060214/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

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